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A Lesson in Survival: *S. aureus* versus the Skin

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Staphylococcus aureus **epidemic strain USA300 is a highly successful pathogen. However, the underlying basis of this success is not clear. Now, Thurlow and colleagues (2013) provide evidence linking the bacterial arginine catabolic mobile element (ACME) to the dominance of USA300 as a pathogen of the skin.**

Human skin provides a physical barrier and first line of immunological defense against noxious stimuli and harmful insult. External layers of the skin are particularly inhospitable to pathogenic microbes. The low moisture content, marked acidity, and abundance of resident microbes on the outer layers of the skin, the epidermis, provide a physical barrier that can keep the most successful pathogens at bay (Miller and Cho, 2011). If an organism breaches these physical barriers, the skin has the capacity to recognize molecular determinants of pathogenic microbes to facilitate host cell signaling and immune cell chemotaxis, thereby bolstering the immune response and providing an additional level of defense (Miller and Cho, 2011).

Staphylococcus aureus is a bacterium that is capable of rapid adaptation to host insult in order to promote survival in disparate conditions. The organism is notorious for its ability to cause skin and soft tissue infections. Through gene acquisition and alterations in regulatory networks, *S. aureus* is able to counter the physical and immunological barriers of the skin. Some of its defense tactics include the production of specialized binding proteins, immune evasion molecules, and immune cell targeting toxins (Foster, 2005). As a result, *S. aureus* has become one of the leading causative agents of skin and soft tissue infections. Its environmental adaptability coupled with an increase in antibiotic resistance among infectious isolates make *S. aureus* a major public health concern.

S. aureus strains exhibit periodic shifts in the clonal lineage responsible for widespread disease (Li et al., 2009). In the USA, the current epidemic strain of methicillin-resistant *S. aureus*, MRSA, is the sequence type 8 strain, USA300. Considerable attention has been given to the analysis of USA300 virulence and the factors responsible for its rise to dominance in both community and clinical settings (Li et al., 2009; Montgomery et al., 2008). Indeed, well-known virulence factors such as alpha hemolysin, phenol soluble modulins (PSMs), and the Panton-Valentine leukocidin are produced at higher levels in these strains (Li et al., 2009). Additionally, USA300 isolates have higher activities of gene regulatory systems including the accessory gene regulatory system Agr (Li et al., 2009). While increased Agr activity and enhanced production of toxins are likely to contribute to the overall pathogenic potential of USA300, they do not fully explain its propensity to cause skin and soft tissue infection.

An additional genetic locus harbored by USA300 strains is the arginine catabolic mobile element (ACME). ACME is a 33-gene locus that contains genes important for arginine catabolism (*Arc*), an oligopeptide permease system (*opp3*), and a polyamine N-acetyl transferase (*speG*). In USA300, ACME is genetically linked to the staphylococcal chromosomal cassette *mec* (SCC*mec*) type IVa (Diep et al., 2008). SCC*mec* confers β-lactam resistance to *S. aureus*. The genetic linkage between SCC*mec* and ACME was observed by Diep et al. and is believed to be present in nearly all USA300 isolates (Diep et al., 2008). It was postulated that the presence of ACME, which confers a modest fitness advantage to USA300, coupled with the antibiotic resistance associated with SCC*mec* typeIVa could provide a suitable explanation for the increased dominance of USA300. However, additional studies have demonstrated that the increased fitness of ACME-containing USA300 strains may not necessarily lead to an increase in virulence (Montgomery et al.,

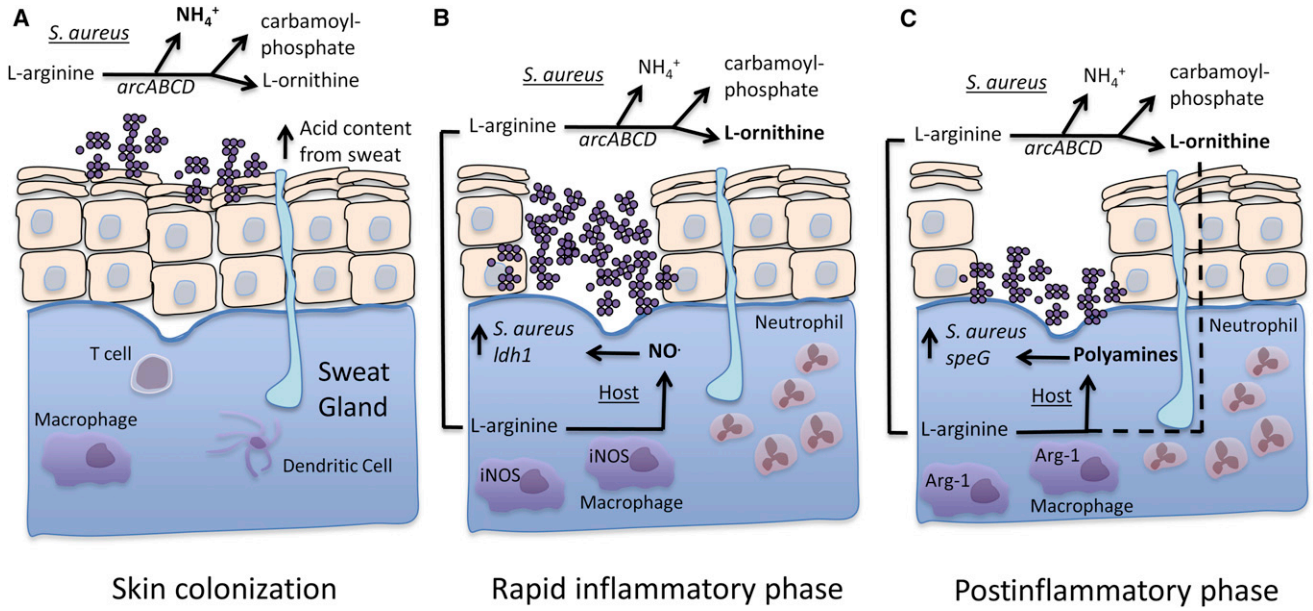

Figure 1. Simplified Schematic of the Contribution of ACME to *S. aureus* USA300 Survival on and within Human Skin

(A) Skin colonization by *S. aureus* is facilitated by neutralizing the acidic pH of human sweat via the production of ammonia (NH_4^+) from L-arginine catabolism. (B) Upon breaching the epidermal layer, a rapid inflammatory phase begins. Neutrophils and iNOS-producing macrophages are recruited to the site of infection. iNOS uses L-arginine to produce NO· to fight infection. *S. aureus* counters this innate immune attack via upregulation of the nitric oxide-inducible lactate dehydrogenase (*ldh1*). Excess L-arginine is scavenged by *S. aureus*, depleting arginine pools from the host and increasing L-ornithine as a by-product. (C) As infection proceeds, a postinflammatory phase begins. Expression of Arg-1 by host macrophages leads to the synthesis of polyamines, which are critical for wound healing and toxic toward most *S. aureus* strains. USA300 uses the ACME-encoded *speG* to counter polyamine toxicity. *S. aureus* continues to scavenge L-arginine and produces L-ornithine as a product of its catabolism. The increased L-ornithine feeds into host-derived polyamine synthesis pathways, further necessitating SpeG for *S. aureus* survival.

2009). Montgomery et al. demonstrated that there is no pathologic difference between ACME-containing USA300 strains and those that do not contain the element in rat pneumonia and murine skin and soft tissue infection models (Montgomery et al., 2009). It would appear from these studies that enhanced fitness does not necessarily equate to enhanced virulence.

A manuscript by Joshi et al. recently provided additional insight into the functional role of genes encoded within ACME (Joshi et al., 2011). *S. aureus* is one of a number of bacterial species that lack the ability to synthesize polyamines. Polyamines are aliphatic compounds, many of which are synthesized from L-arginine, that facilitate countless cellular functions including wound healing and inflammation. Interestingly, the majority of *S. aureus* clones are sensitive to exogenous polyamines in culture, except for USA300 (Joshi et al., 2011). In their studies, the authors link polyamine resistance in USA300 to the polyamine *N*-acetyltransferase SpeG, encoded on ACME. The acquisition of polyamine resistance through SpeG was intriguing; however, the study did not demonstrate a role for polyamine resistance in *S. aureus* pathogenesis. Thus, while functional activities are being assigned to gene products within ACME, we still do not know what role this element may have in the pathogenesis of USA300.

In this issue of *Cell Host & Microbe*, Thurlow and colleagues (Thurlow et al., 2013) now provide evidence that links the functional activities of ACME genes with the virulence of USA300 during skin and soft tissue infections. As described, the skin provides a formidable barrier to infection, yet recent evidence suggests an ability of USA300 to colonize this niche at higher rates than other strains (Miko et al., 2012). One of the key physical features preventing bacterial colonization of the skin is its acidic pH (Figure 1). In this work, the authors use broth culture viability studies to demonstrate that the arginine deiminase system encoded by ACME (Arc) is responsible for the enhanced acid tolerance of USA300 in the presence of exogenous lactic acid, the major organic acid present on human skin. Arc increases the production of ammonia from L-arginine catabolism, thereby countering this acidic stress (Figure 1). The authors further demonstrate that the constitutive activity of ACME-Arc drives ammonia production regardless of the presence of glucose or oxygen, a unique feature of ACME that sets it apart from the arginine deiminase system encoded in the chromosome of all *S. aureus* strains. Thus, through ACME, USA300 is better able to resist the acidic environment of skin, implying a unique colonization advantage for this strain.

Once the skin is colonized, *S. aureus* can breach the epidermis, leading to skin and soft tissue infections. Hallmarks of these infections include a rapid pro-inflammatory phase marked by the infiltration of large numbers of phagocytic leukocytes. This phase is characterized by abundant production of NO· (derived from L-arginine) by host phagocytes to which *S. aureus* strains are known to be resistant (Richardson et al., 2008) (Figure 1). A postinflammatory phase then follows, characterized by an increased production of polyamines from L-arginine via the upregulation of host-derived Arginase-1 (Arg-1) (Figure 1). Increased

production of polyamines is normally restrictive to *S. aureus* growth, given the sensitivity of most strains to these molecules (Joshi et al., 2011). However, USA300 strains contain ACME-encoded *speG*, which confers resistance to polyamine toxicity in vitro (Joshi et al., 2011). Here, the authors extend this finding using in vivo models to demonstrate that *speG* mutants in USA300 display increased sensitivity to polyamines during the postinflammatory phase of skin and soft tissue infection. Further, their data indicate that bacterial burden in late-stage abscesses is largely dependent on SpeG, a novel finding that links ACME to persistence during skin and soft tissue infection.

Thurlow et al. continue their investigation into the role of ACME in skin infections by addressing an apparent paradox between their findings and that of earlier studies, which were unable to uncover a role for ACME in skin and soft tissue infections (Montgomery et al., 2009). The authors demonstrate that if *speG* is deleted, bacterial burden is significantly reduced and clearance occurs more quickly in vivo. However, it was previously observed that an ACME mutant (lacking *speG* and *arc*) is equally as virulent as an ACME-containing strain (Montgomery et al., 2009). Thus, it is somewhat perplexing that an ACME mutant is not also attenuated in vivo. Through the use of murine infection models, the authors rationalize these findings by demonstrating that *S. aureus* Arc diverts L-arginine away from NO· production by the host, thereby fostering polyamine synthesis, a result of the increased production of L-ornithine by the bacterium (Figure 1). The presence of Arc appears to enhance host polyamine production and requires SpeG to detoxify the system. Indeed, deletion of *arc* in a *speG* mutant increases the virulence of the strain to WT levels. Thus, the fitness advantage conferred upon USA300 via ACME requires both Arc and SpeG.

All together, the work presented in this new study both describes a novel role for ACME as an important virulence determinant in USA300 skin and soft tissue infection and provides a unique rationale for how this strain may have rapidly outcompeted other *S. aureus* clones for dominance over the human skin niche. Furthermore, it highlights the remarkable adaptability of *S. aureus* in the face of host immunity, one that extends beyond traditional mechanisms of pathogenesis (toxins, immune-modulatory molecules, etc.). It is worth mentioning that these findings do not discount the role of major virulence factors in *S. aureus* skin and soft tissue infections; rather, they add to the ever-evolving armament of *S. aureus* survival mechanisms.

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How *Trypanosoma cruzi* Feasts upon Its Mammalian Host

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Trypanosoma cruzi has a complex relationship with its mammalian host in which parasite and host metabolic networks are intertwined. A genome-wide functional screen of *T. cruzi* infection in HeLa cells (Caradonna et al., 2013) divulges host metabolic functions and signaling pathways that impact intracellular parasite replication and reveals potential targets for therapeutic exploitation.

Chagas' disease is a devastating, pernicious, and often fatal disease of the cardiovascular system for which the hemoflagellate protozoan parasite, *Trypanosoma cruzi*, is the etiologic agent. The neurological system and digestive tract can also be impacted by *T. cruzi* infection. Chagas' disease is endemic to all 22 countries of South and Central